Result Page

Taxane containing pharmaceutical preparation and procedure for its production description background of the invention the invention concerns a new Taxane containing pharmaceutical preparation, a manufacturing process for this pharmaceutical preparation and their use in particular for intravenous application.

Taxane are anti-carcinogenic medicaments, which possess structurally a Taxankern, that from <a RTI ID=1.1> Diterpene Kohlenstoffgerüst< /RTI> exists (M. T. Huizing et al. : CAN cerium Investigation 13, S. 381404 <RTI ID=1.2> (1995)).</RTI>

Its most important representative is Paclitaxel (Taxol) and Docetaxel.

Taxane such as z. B. Paclitaxel and Docetaxel become with oral administration only much <RTI ID=1.3> badly< /RTI> absorbed and is given therefore by means of intravenous infusion.

Taxane are only <RTI ID=1.4> few< /RTI> water-solubly. This leads to <RTI ID=1.5> serious< /RTI> problems in the use of Taxanen, there a simple water-soluble pharmaceutical preparation not <RTI ID=1.is >possible< for 6> /RTI.

The pharmaceutical formulations for the intravenous use of Taxanen, used so far, contain as <RTI ID=1.7> solvents< /RTI> large quantities of not ionischen emulsifying agents such as z. B.

<RTI ID=1.8> Polyoxyethylen castor-oil,< /RTI> Polysorbat as well as alcohol.

Thus for example a RTI <ID=1 contains.9> commercial< /RTI> formulation in a Milliliter only 6 mg Paclitaxel, but 520 mg <RTI ID=1.10> Polyoxyethylen castor-oil< /RTI> and 450 mg <RTI ID=1.11> ethylen alcohol.</RTI>

Another pharmaceutical formulation contains 20 mg Docetaxel, RTI ID=1 in <a Milliliter.12> solved< /RTI> in the not ionischen emulsifying agent Polysorbat 80.

The available pharmaceutical formulations are connected, there with numerous serious disadvantages with the administration of the pharmaceutical effective quantities of Taxanen in <RTI ID=2.1> height< of /RTI> of approx. 200-500 mg per application approx. 20-40 g of the not ionischen emulsifying agents to be given.

The formulations prepare problems with the handling, there it before application with other infusion solutions such as z. B.

Common salt, glucose to be diluted must. This <RTI ID=2./RTI> leads< 2> to problems with <the RTI ID=2.3> stability< /RTI> <RTI ID=2.4> (precipitation< /RTI> of the active substance).

In addition <RTI ID=2.5> must <be used> /RTI filter systems.

<RTI ID=2.6> plastic containers< /RTI> <RTI ID=2.7> may not <be used> /RTI.

▲ top The problems are still more serious due to side effects of the used not ionischen <RTI ID=2.8> solvents.</RTI>

Since these heavy anaphylaktische shocks can release, a RTI ID=2 is before <application.9> Prämedikation< /RTI> with Kortikosteroiden, Antibistaminika and H2-Antagonisten necessarily. <The RTI ID=2.In addition> 10< solvents> /RTI are nephrotoxisch, celltoxic and kardiotoxisch. They have besides an unfavorable influence on the Pharmakokinetik and the distribution of Taxanen in the organism. Probably the used RTI <ID=2 reduces.11> solvent< /RTI> even the clinical effectiveness of the Taxane.

There <the RTI ID=2.12> for< /RTI> Taxane used <RTI ID=2.13> solvents< /RTI> <a RTI ID=2.14> crucial< /RTI> portion of the side effects of the Taxane and/or. their effectiveness have, is the development <RTI ID=2.15> more alternatively,< /RTI> <RTI ID=2.16> improved< /RTI> Darreichungsformen, which are to contain in particular no or only small quantities of not ionischen emulsifying agents, of crucial importance and a pharmaceutical challenge (see. in addition: J. M. Meerum Terwogt et al. : Alternative formulation OF paclitaxel. CAN cerium Treatment Reviews 23, 87-89 (1997) as well as J. D. Adam's et al. : Taxol: A History OF Pharmaceutical development and Current Pharmaceutical Concerns.

Monogr. Natl. CAN cerium Invest. 15, 141-147 (1993); J. D. Jonkman< RTI ID=2.17> of deVries< /RTI> et al. : Pharmaceutical development OF (Investigational) anti-CAN cerium Agents for parenterally Use A Review. Drug Develop. Indust. Pharmacy 22, 475 (1996)).

In the following the most important alternative Darreichungsformen of Taxanen is described briefly. None this Darreichungsformen stands however so far as certified medicament to <the RTI ID=2.18> order.</RTI>

<RTI ID=3.1> water-soluble< /RTI> <RTI ID=3.2> preliminary stages< /RTI> (pro Drugs) one tries, by chemical changes in <the RTI ID=3.To make> water soluble< 3> molecule /RTI the Taxane. This is difficult and <RTI ID=3.4>

extremely< /RTI> complex. Besides <RTI ID=3.5> can <be changed> /RTI the characteristics of the Taxane in unfavorable way. Since it concerns new materials, a complete new development of the medicament in addition is necessary.

<RTI ID=3.6> CO solvents< /RTI> Paclitaxel <RTI ID=3./RTI> separates< 7> in <RTI ID=3.8> solvents< /RTI> such as ethanol, Dimethylsulfoxid or polyethylene glycol 400 (PEG 400). With the necessary dilution to the infusion the Taxane falls however both in the infusion solution and in the blood and loses besides at effectiveness (J. M. Meerum Terwogt et al. : Canc. Treatment Rev. 23, 87-95 (1997), as well as J. D.

Adam et al. : Monogr. Natl. CAN cerium Inst. 15, 141-147 (1993)).

Complex one with Cyclodextrinen by integration with Cyclodextrinen knows <the RTI ID=3.9> solubility< /RTI> von Taxanen <RTI ID=3.10> increases< /RTI> become (And. S. Sharma et al. : To. Chem. one.

Soc. To. Pharm. ASS. 84, 1223-1230 (1995)). The solutions however viscously and contain firm particle. Besides is <the RTI ID=3.To give> 11< solubility> /RTI highly enough around a sufficient quantity of active substance.

Liposome and Mizellen Liposome are carrier systems, which consist of one or more fat-similar diaphragms, which include an aqueous phase. These carrier systems <RTI ID=3.12> knows< /RTI> <RTI ID=3.13> fat-soluble< /RTI> substances into the diaphragms take up and make so an intravenous application possible. With Taxanen, in particular Paclitaxel, were developed numerous liposomale Darreichungsformen (see. in addition: J. Meerum Terwogt et al. : CAN cerium Treatment Review 23, 83-87 (1997)).

Liposomen are however extremely wärme-und heat sensitive.

It <RTI ID=4.1> /RTI< cannot > be heat-sterilized therefore, like this <RTI ID=4.2> for< /RTI> infusion solutions one demands. They are unstable also with the storage. In the necessary larger quantities they are to be manufactured only at large expenditure sterile. None of the numerous developed liposomalen forms was developed therefore so far to production-ready ones.

Mizellen, z. B. from Gallensalzen and Phospholipiden with Paclitaxel were loaded and made then of it Liposome.

Such Mizellen is unstable, sterilization is difficult and production in larger yardstick very much <RTI ID=4.3> complicates.</RTI>

Fat emulsions contrary to Liposomen consist fat emulsions of <a RTI ID=4.4> oil in water< /RTI> emulsion, whereby that is surrounded 01 for stabilization with one or more emulsifying agents. The kind of the production as well as the used oil and the assigned emulsifying agents are crucial for <the RTI ID=4.5> quality< /RTI> von Fettemulsionen, there numerous emulsifying agents, in particular the frequently used not ionischen emulsifying agents, is toxic and with fat emulsions <the RTI ID=4.6> size of< /RTI> of the fat particles generally below 5 Micron, best under 1, 5 Micron to be is (P. K. Hansrani et al. : J. Parent. <RTI ID=4.7> Sci.</RTI> Technol. 4, 145 -150 (1983)).

The use from fat emulsions to <the RTI ID=5.1> increase< /RTI> <of the RTI ID=5.2> solubility< /RTI> and Stabilität von Taxanen <RTI ID=5.3> /RTI< appears> first in principle <RTI ID=5.4> possible.</RTI> in fat emulsions becomes usually <RTI ID=5.5> Sojaöl< /RTI> as fat uses. After J. M. Meerum Terwogt et al. (CAN cerium Treatment Review 23, 87-95 (1997)), as well as J. D. Adam's et al. (Monogr. Natl. CAN cerium Inst. 15, 141-147 (1993)) is the use of <RTI ID=5.6> Sojaöl< /RTI> not <RTI ID=5.7> possible,< /RTI> there itself Taxane in <RTI ID=5.8> Sojaöl< /RTI> not sufficiently <RTI ID=5.9> solve.</RTI> becomes the RTI <ID=5 in such a way.10> solubility< /RTI> von Paclitaxel in <RTI ID=5.11> Sojaöl< /RTI> indicated as only 0, 3 mg/ml.

It is determined therefore, <RTI ID=5.12> that< /RTI> with Taxanen the use simple oil in water emulsions such as z. B. the commercial emulsions with Sojaöl, Intralipid, not <RTI ID=5.is >possible< for 13> /RTI. <RTI ID=5.14> Sojaöl< /RTI> is a Triglycerid, fatty acids with 16-18 carbon atoms <the RTI ID=5.,> /RTI contains< 15> such as palmitic acid, <RTI ID=5.16> Linolensäure,< /RTI> <RTI ID=5.17> Linolsäure< /RTI> and Ölsäure.

One tried to manufacture fat emulsions with Taxanen by use of special carrier materials and emulsifying agents.

In the WHERE 96/02247 a Taxane is containing oil in water emulsion described, which at least a Taxan contains, 01, water and an surface-active means. During the production <RTI ID=5.18> must </RTI> <RTI ID=5.19> CO solvents< /RTI> such as alcohols to be used, those afterwards in a complex process be again removed <RTI ID=5.20> must.</RTI> already smallest residues in the final product <RTI ID=5.21>< would prevent> /RTI an intravenous application.

Also salts of free fatty acids are not added. The received emulsion is not heat sterilizable; consequently a such heat sterilization is also not described.

B. D. Tarr et al. (Pharmaceutical Res. 4, 162-165 (1987)) describe an emulsion, those beside water 1 <RTI ID=5.22> % < /RTI> Paclitaxel, 50 <RTI ID=5.23> %< /RTI> tri monacetin, 2, 0 <RTI ID=5.24> %< /RTI> oleic acid ethyl esters, 1, 5 <RTI ID=5.25> %< /RTI> Pluronic F 68 and 1, 5 <RTI ID=5.26> %< /RTI> Sojalecithin <RTI ID=5.27> contains.</RTI> although the emulsion was not heat-sterilized, rose with the storage the average <RTI ID=5.28> particle size< /RTI> of at the beginning of 1 Micron already after 2 months on 4 Micron on and after 6 months was to be observed 2 phases, i.e. it was missing no more emulsion. The emulsion <RTI ID=6.1> did not prove< /RTI> as toxic and the formulation showed up <RTI ID=6.2> anti-tumor activity< /RTI> more. The component of Pluronic F 68 is besides a synthetic nichtionischer emulsifying agent with toxic effects.

B. Lundberg (J. Pharm. Pharmacol. 49, 16-21 (1997)) the production of a fat emulsion describes RTI ID=6 as carrier <for medicaments.3> among other things for< /RTI> Paclitaxel. Triolein (Glyceroltrioleat) became, the Triglycerid <of the RTI ID=6.4> oleic acid,< /RTI> as carriers used, as emulsifying agents was used Dipalmitoyl Phosphatidylcholin in combination with the not ionischen emulsifying agent Polysorbat 80. <RTI ID=6.5> additional< /RTI> had to <the RTI ID=6.6> increase< /RTI> <of the RTI ID=6.7> solubility< /RTI> and for stabilization still polyethylene glycol to be used.

The emulsion can not be heat-sterilized, but must by complex dialysis procedures be cleaned. The emulsion had to be stored in lypholysiertem condition. It is only after <the RTI ID=6.8> diluting< /RTI> with infusion solutions like common salt or glucose solution applicable. The emulsion <RTI ID=6.9> /RTI< unphysiologische> , toxic emulsifying agents contains such as Polysorbat of 80 and unphysiologische substances such as polyethylene glycol.

<RTI ID=6.10> Dipalmityol Phosphatidylcholin< /RTI> is extremely expensive. <The RTI ID=6.11> particle size< /RTI> is besides with 20-40 Micron to <RTI ID=6.12> largely.</RTI> the production is complicated and extremely complex. B. In addition Lundberg determines, <RTI ID=6.13> that< /RTI> both the use of tri monacetin and Tributyrin an unstable emulsion <RTI ID=6.,> /RTI results in< 14> during Tricaproin and Tricaprylin comparably with Triolein in the bad <RTI ID=6.15> solubility< /RTI> von Paclitaxel and in the emulsion formation is. It is stated that <the RTI ID=6.16> solubility< /RTI> von Paclitaxel in Triolein and in <RTI ID=6.17> Sojaöl< /RTI> with approx.

0, 3 mg/ml is too small, around <RTI ID=6.To use> 18< Sojaöl> /RTI or the commercial fat emulsion Intralipid as carriers for Paclitaxel.

The formulation and the production of pharmaceutical preparing from Taxanen to the intravenous infusion is therefore a serious problem (B. Lundberg, J. Pharm.

Pharmacol. 49, 16-21 (1997)). Stable and sterile Darreichungsformen, those in addition also still in the technical yardstick are manufactured <RTI ID=6.19> does not know< /RTI> and unphysiologischen, side effect-rich <RTI ID=6.20> solvents,< /RTI> <RTI ID=7.1> solution mediator< /RTI> and Emulgatoren contain, do not stand so far not to <the RTI ID=7.2> order.</RTI> besides does not give it Darreichungsformen, those without previous diluting with infusion solutions <to RTI ID=7.3> infused< /RTI> becomes <RTI ID=7.4> can.</RTI>

Although for more than ten years admits the described problems are and therefore for a long time on it one works, so far despite all efforts, a suitable infusion solution to intravenous application RTI <ID=7 did not succeed.to develop> 5< for> /RTI Taxane. In particular no Taxane knew containing fat emulsion to <the RTI ID=7.6> order< /RTI> to be placed.

Summary of the invention a goal <RTI ID=7.7> of available< /RTI> invention is therefore a Taxane containing pharmaceutical Darreichungsform in form <of a RTI ID=7.8> oil< /RTI> in water emulsion, which is suitable for intravenous application also.

<The RTI ID=7.no> synthetic< not ionischen> RTI ID=7 essentially contains 9 /RTI according to invention <pharmaceutical Darreichungsform.10> emulators,< /RTI> for example <RTI ID=7.11> Polyoxyethylen castor-oil,< /RTI> hydrogenated <RTI ID=7.12> Polyoxyethylen castor-oil< /RTI> ; Polysorbate, Pluronic etc. In a further execution form of the invention are also no halfsynthetic or natural-prove occurring not ionische emulsifying agents, which possess toxic side effects, contained. The composition of the invention is more near characterized in the requirement 1.

The disadvantages of the Darreichungsformen used so far become z. B. avoided by the production of a Taxane containing <RTI ID=7.13> infusion solution,< /RTI> in which the Taxane in a therapeutically effective quantity are contained of free fatty acids and water, in an emulsion, consisting of Triglyceriden of fatty acids with 2-22 carbon atoms, prefer 4-20 carbon atoms, 3-sn Phosphatidylcholin, alkali salts.

Apart from the absence of synthetic not ionischen emulsifying agents the Darreichungsform according to invention has further <RTI ID=8.1> advantages< to handle> /RTI simple there it is, in larger quantities industrially in sterile form to manufacture is and an excellent <RTI ID=8.2> stability< /RTI> possesses.

<The RTI ID=8.3> expression " in< /RTI> substantial no synthetic ionischen emulsifying agents " does not mean, <RTI ID=8.4> that< /RTI> small quantities of synthetic not ionischen emulsifying agents are present <RTI ID=8.5> can do,< /RTI> if this no unfavorable effects on the patient unfold. Synthetic not ionische emulsifying agents <RTI ID=8.6> knows< /RTI> in a quantity of < <RTI ID=8.RTI> ID=8 prefers< 7> 5g/l < <, /RTI.8> lg/1,< /RTI> more preferentially < 0, 5 g/l and further prefers < 0, 3 g/l are present. In particular preferentially the formulation does not contain synthetic not ionischen emulsifying agents, moreover preferentially the formulation does not contain other not ionischen emulsifying agents with harmful side effects.

The Phosphatidylethanolamin can in the pharmaceutical preparation according to invention in a quantity of 0, 01 to 3 <RTI ID=8.9> thread.- 0,< 01-2> RTI ID=8 prefer % <, /RTI.10> thread.- %,< /RTI> more preferentially 0, 05-2 thread. <RTI ID=8.11> %,< /RTI> are present.

<RTI ID=8./RTI> description<> of the invention detailed 12 with <the RTI ID=8.it> concerns< 13> /RTI according to invention Darreichungsform in particular a fat emulsion for intravenous application, which Taxane, Triglyceride with 2-22 carbon atoms, 3-sn - Phosphatidylcholin, alkali salts of free fatty acids and water contains.

Additionally the Darreichungsform can contain still of Phosphatidylethanolamin as well as substances, which make the emulsion blood isotone like z. B. Glycerin and/or Sorbit and/or Xylit.

Fat emulsions for parenteral application and procedures for their production are well-known. (See. in addition: DE-PS 1 1249 454, GP-PS 2,406,621, DE-OS 3,721,137, EP 071,995, DE-OS 3,032 ,300, US 5,589,508) these fat emulsions are 01 in water emulsions, in those <the RTI ID=9.1> particle size< /RTI> <of the RTI ID=9.2> droplets< /RTI> less than 5 Micron, thus RTI <ID=9 amounts to.3> that< /RTI> the emulsions without the risk of the occurrence of Embolien are infused <RTI ID=9.4> can.</RTI>

Also fat emulsions, the medicaments z. B. Cyclosporine, contained, are well-known. (See. in addition: US 5,527,537, US 5,622,714) the used oils are for example <RTI ID=9.5> Sojaöl,< /RTI> <RTI ID=9.6> thistle oil,< /RTI> <RTI ID=9.7> olive oil,< /RTI> <RTI ID=9.8> Fischöle< /RTI> and mittelkettige Triglyceride.

Preferably MCT oils become alone or in combination with <RTI ID=9.9> Sojaöl< /RTI> or Olivenöl uses. As emulsifying agents Phosphatidylcholine become out and/or. Sojalecithin uses. The oils are emulsified with the emulsifying agents,

until a PartikelgröRe of the fat particles will receive from smaller than 5 Micron.

Alcohols, like methanol, are according to invention contained ethanol and isopropanol, not in the pharmaceutical preparation and/or. with the production of the pharmaceutical preparation are not used.

As described before, RTI ID=9 becomes futile for more than <ten years.tries> 10 to manufacture< Taxane> /RTI containing fat emulsions and/or. Taxane containing fat emulsions without the use <RTI ID=9.to manufacture> 11< of not ionischer> /RTI emulsifying agents.

In addition, RTI <ID=9 was so far determined.12> that< /RTI> itself Taxane, z. B.

Paclitaxel in Triglyceriden of fatty acids with a chain length of 6-18 carbon atoms not sufficiently solve, in order to achieve therapeutically effective concentrations. In Tributyrin <RTI ID=9.><a somewhat> higher RTI ID=9 resulted 13 (fatty acid /RTI with 4 <carbon atoms).14> solubility,< /RTI> however despite use of not ionischer emulsifying agents no sturdy emulsion could be manufactured. (B. D. Tarr et al. : Pharmaceutical Research 4, 162-165 (1987); B. Lundberg: J.

Pharm. Sci. 83, 72-75 (1994); Int. Journ. Pharmaceutics 134, 119-127 (1996); J. Pharm. Pharmacol. 49, 16-21 (1997)) <RTI ID=10.1> surprisingly< /RTI> became according to the invention <RTI ID=10.2> found,< /RTI> <RTI ID=10.3> that< /RTI> it very probably <RTI ID=10.4> possible< /RTI> is not to manufacture one preferentially intravenously applicable Darreichungsform with Taxanen not ionischen emulsifying agents <RTI ID=10.5>, /RTI< contains> in form of a Taxane containing emulsion, which consists of Triglyceriden preferentially by fatty acids with 2-22 carbon atoms, with 4-20 carbon atoms, 3-sn Phosphatidylcholin, alkali salts of free fatty acids and water.

It is crucial thereby, <RTI ID=10.6> that< /RTI> the Taxane first in the used Triglycerid and/or Triglyceridgemisch <RTI ID=10.7> solved< /RTI> will be emulsified and afterwards using 3-sn Phosphatidylcholin to an emulsion, whose fat particle is predominantly smaller than 5 Micron.

As Taxane prefers Paclitaxel and Docetaxel used. Further is <RTI ID=10.8> according to invention< /RTI> the following Taxane usable: <RTI ID=10.9> Spicatin; </RTI> Taxan-2, 13-dione, 5. beta., 9. beta., 10. beta.tri hydraulic XY, cyclo-9, 10-acetal with acetone, acetate; Taxan2, 13-dione, 5. beta., 9. beta., 10. beta.- tri hydraulic XY, cyclo 9, 10-acetal with acetone; Taxan-2. beta., 5. beta., 9. beta., 10. <RTI ID=10.10> beta.- tetrol,< /RTI> cyclo-9, 10-acetal with acetone; Cephalomannin< RTI ID=10.11> 7-xylosid< /RTI> ; 7-epi-10-Deacetylcephalomannin; 10< RTI ID=10.12> Deacetylcephalomannin< /RTI> ; Cephalomannin; Taxol B; <RTI ID=10.13> 13 (2, 3< /RTI> <RTI ID=10.14> Dihydroxy-3-phenylpropionyl)< /RTI> baccatin III; Yunnanxol; <RTI ID=10.15> 7 - (4< /RTI> Azidobenzoyl) baccatin III; N-Debenzoyltaxol A; <RTI ID=10.16> 0< /RTI> Acetylbaccatin IV; <RTI ID=10.17> 7 - (Triethylsilyl)< /RTI> baccatin III; 7, <RTI ID=10.18> 10-Di-O< /RTI> <RTI ID=10.19> [(2,< /RTI> 2, 2-Trichlorethoxy) carbonyl] baccatin III; Baccatin III< RTI ID=10.20> 13-0-acetat< /RTI> ; Baccatindiacetat; Baccatin; Baccatin VII; Baccatin VI; Baccatin IV; 7-epi-Baccatin III; Baccatin V; Baccatin I; Baccatin III; Baccatin A; 10-Deacetyl-7-epitaxol; Epitaxol; 10-Deacetyltaxol C; 7-Xylosyl-10-deacetyltaxol; 10 Deacetylaxol-7-xylosid; 7-epi-10-Deacetyltaxol; 10 Deacetyltaxol; and 10-Deacetyltaxol B.

The Triglyceride contains fatty acids with 2-22 carbon atoms.

So <RTI ID=10.21> can <be used> /RTI for example the Triglyceride of the following fatty acids: Designation <RTI ID=11.1> number of fatty acids< of /RTI> of the carbon atoms tri monacetin 2 Tributyrin 4 Tricaproin 6 Tricaprylin 8 Tricaprin 10 Trilaurin 12 Trimyristin 14 Tripalmitin 16 Tristearin 18 Triolein 18 Trilinolein 18 Trieicosapentain 20 Tridocosahexain 22 it <RTI ID=11.2> can <be used> /RTI also mixtures of these Triglyceride and/or naturally occurring <RTI ID=11.3> and/or< /RTI> refined and/or umgeesterte Triglyceride of natural oils like mittelkettige Triglyceride (MCT oils), <RTI ID=11.4> Sojaöl,< /RTI> <RTI ID=11.5> thistle oil,< /RTI> olives, <RTI ID=11.6> Fischöl< /RTI> etc. and/or mixtures of these Triglyceride.

Also Triglyceride of hydrogenated fatty acids are usable.

Triglyceride and/or Triglyceridgemi of fatty acids with 4-20 carbon atoms are preferential.

It is pointed out that Tributyrin apparent works anti-carcinogenically, and which effect of Taxanen can increase synergistically.

As raw materials <RTI ID=12.1> for< /RTI> 3-sn-Phosphatidylcholin prefer Eilecithine and Sojalecithine are applicable.

Lecithine with a content of 3-sn-Phosphatidylcholin of more than 60 <RTI ID=12.2> %< /RTI> are preferential. Particularly preferentially is with a content of Phosphatidylcholin from 60 to 90%.

The 3-sn-Phosphatidylcholin can be also partial or completely hydrogenated. The used Lecithine <RTI ID=12.3> can <contain> /RTI beside 3-sn-Phosphatidylcholin also of Phosphatidylethanolamin.

During z. B. in the preparation of the WHERE 96/2247 approx. 20 mg Cholesterin/ml Triglycerid are contained, prefer <the RTI ID=12.4> /RTI< according to invention> preparation quantities far under 10 mg, more preferentially under 5 mg, z. B. approx. <RTI ID=12.5> 1< /RTI> mg <RTI ID=12.6> Cholesterin/ml< /RTI> Triglycerid.

Further is an alkali salt of a fatty acid with <RTI ID=12.7> 4-24< /RTI> carbon atoms contain, around the pH value of the emulsion on 5-9 <RTI ID=12.8> to adjust< /RTI> and emulsifying and the homogenization facilitate. Thereby fatty acids with 12-22 carbon atoms are preferential, especially are prefer fatty acids with 16-20 carbon atoms. The alkali salt of a fatty acid knows also in situ by addition of an alkali hydroxide into a mixture, a fatty acid <the RTI ID=12.,> /RTI contains< 9> to be manufactured. Sodium or potassium salts of <RTI ID=12.10> palmitic acid,< /RTI> oleic acid, <RTI ID=12.11> Linolsäure< /RTI> and Linolensäure is particularly preferential. The concentration of the Triglyceride in <the RTI ID=12.12> /RTI< according to invention> Darreichungsform RTI <ID=12 amounts to.13> 1 60%.</RTI> preferentially are concentrations of 3-40 <RTI ID=12.14> %.</RTI>

The concentrations of the used emulsifying agent in the form of and/or Sojalecithin amount to 0, 2-4 <RTI ID=12.15> %,< /RTI> preferentially are concentrations of 0, 4-2, 5%, whereby the concentration of the emulsifying agent depends

on the concentration of the Triglyceride. If assigned, the concentrations of the alkali salts of the fatty acids amount to generally 0, 01-0, 2 <RTI ID=12.prefer> 16 %<,> /RTI 0, 02-0, 1 Gew%.

The used Taxane should be present in therapeutically effective concentrations. Generally these concentrations amount to 0, 01-0, 3 <RTI ID=13.1> %< /RTI> (0, 1-3 mg/ml).

In order blood isotones an emulsion too receive, <RTI ID=13.2> knows< /RTI> well-known isotonisierende substances such as z. B. Glycerin, glucose, Fruktose, Sorbit, Xylit contained in the appropriate concentrations its, whereby Glycerin is preferential.

Additionally the pharmaceutical Darreichungsform Vitamin E can contained in the form of Tocopherol or pharmaceutical compatible Tocopherolestern, in order to work as stabilizing anti-oxide to. The used concentrations amount to about 0, 15 to 1, 5 Gew%, dependent on kind and content of the used Triglyceride and emulsifying agents.

<The RTI ID=13.3> particle size< /RTI> of the fat particles in the oil in waters emulsion is <RTI ID=13.4>< /RTI> as smaller as possible than 5 Micron. At least 97 <RTI ID=13.5> %< /RTI> of the particles should be smaller than 5 Micron. Generally <RTI ID=13.6> /RTI<> the RTI <ID=13 amounts to.1-1> Micron<, > Micron prefers 7 particle size /RTI on the average 0, between 0, 2-0, 6.

Since not all fat particles are equally large, typical distributions of the particles, z result. B. : <RTI ID=14.1> particle size< /RTI> number of particles < 0, 2 Micron 34 <RTI ID=14.2> %< /RTI> 0, 2-0, 5 Micron 43 <RTI ID=14.3> % < /RTI> 0, 5-0, 9 Micron 14 <RTI ID=14.4> %< /RTI> 0, 9-1, 2 Micron 6 <RTI ID=14.5> %< /RTI> 1, 2-1, 9 Micron 2% 1, 9-2, 2 Micron less than 1 <RTI ID=14.6> %< /RTI> 2, 2-2, 5 Micron less than 1 <RTI ID=14.7> %< /RTI> 2, 5-3, 2 Micron less than 1% > 3, 2 Micron less than 1% <RTI ID=14.8> possible ones </RTI> suitable <RTI ID=14.9> /RTI< according to invention> pharmaceutical Darreichungsformen as emulsions have the for example following composition: Tributyrin 10 <RTI ID=14.10> g/100< /RTI> ml Glycerin (to the Isotonisierung) 2, 5 <RTI ID=14.11> g< /RTI> 100 ml 1, 2 <RTI ID=14.12> g/100< /RTI> ml sodium oleate 40 <RTI ID=14.13> mg/100< /RTI> ml Paclitaxel 100 mg/100 ml water <RTI ID=14.14> (for< /RTI> injection purposes) ad 100 ml or: Mittelkettige Triglyceride 10 <RTI ID=14.15> g/100< /RTI> ml consisting predominantly of Capryl and Caprinsäure Glycerin 2, 5 <RTI ID=14.16> g/100< /RTI> ml , containing approx. 80 <RTI ID=14.17> %< /RTI> 1, 5 <RTI ID=14.18> g< /RTI> 100 ml 3-sn-Phosphatidylcholin potassium oleate 50 <RTI ID=15.1> mg/100< /RTI> ml Paclitaxel 100 mg/100 ml water <RTI ID=15.2> (for< /RTI> injection purposes) ad 100 ml or: Tributyrin 5 <RTI ID=16.1> g/100 ml< /RTI> Tricaproin 5 <RTI ID=16.2> g/100< /RTI> ml Mittelkettige Triglyceride 5 <RTI ID=16.3> g/100< /RTI> ml (predominantly fatty acids with 8 and 10 carbon atoms) Glycerin 2, 5 <RTI ID=16.4> g/100< /RTI> ml 0, 8 <RTI ID=16.5> g/100< /RTI> ml sodium oleate 50 <RTI ID=16.6> mg/100< /RTI> ml Docotaxel 40 <RTI ID=16.7> mg/100< /RTI> ml water <RTI ID=16.8> (for< /RTI> injection purposes) ad 100 ml or: Mittelkettige Triglyceride 10 <RTI ID=16.9> g/100< /RTI> ml <RTI ID=16.10> Sojaöl< /RTI> 10 <RTI ID=16.11> g/100< /RTI> ml Glycerin 2, 5 g/100 ml 1, 2 <RTI ID=16.12> g/100< /RTI> ml sodium oleate 50 <RTI ID=16.13> mg/100< /RTI> ml Paclitaxel 100 <RTI ID=16.14> mg/100< /RTI> ml water <RTI ID=16.15> (for< /RTI> injection purposes) ad 100 ml or: Tributyrin 4 g/100 ml Mittelkettige Triglyceride 5 <RTI ID=16.16> g/100< /RTI> ml <RTI ID=16.17> Sojaöl< /RTI> 5 <RTI ID=16.18> g/100< /RTI> ml 1, 2 <RTI ID=16.19> g/100< /RTI> ml Glycerin 2, 5 <RTI ID=16.20> g/100< /RTI> ml sodium oleate 50 <RTI ID=16.21> mg/100< /RTI> ml Paclitaxel 120 <RTI ID=16.22> mg/100< /RTI> ml water (for injection purposes) ad 100 ml or: <RTI ID=17.1> Tributyrin 2 g/100< /RTI> ml Mittelkettige Triglyceride 10 g/100 ml <RTI ID=17.2> Fischöl 5 g/100< /RTI> ml 1, 5 <RTI ID=17.3> g/100< /RTI> ml Glycerin 2, 5 g/100 ml potassium oleate 0, 6 <RTI ID=17.4> g/100< /RTI> ml Paclitaxel 80 mg/100 ml water for injection purposes ad 100 ml procedures for the production of the pharmaceutical preparation according to invention for the production of the pharmaceutical preparing according to invention generally as in the following described one proceeds.

<RTI ID=18.1> release< /RTI> (r) of the Taxans (E) in the Triglycerid it was described (B. D. Tarr et al. : Pharmaceutical Research 4, 162-162 (1987); J. D. Adam's et al. : Monogr.

Natl. CAN cerium Inst. 15, 141-147 (1993); B. Lundberg: J.

Pharm. Pharmacol. 49, 16-21 (1997))that itself Taxane not sufficiently in Triglyceriden <RTI ID=18.2> solves< to manufacture> /RTI around thereby emulsions with therapeutically effective concentrations.

As <RTI ID=18.>For example< for> Paclitaxel 0, 3 mg/ml are indicated to 3 solubility /RTI in Triglyceriden with 6-18 carbon atoms.

<RTI ID=18.4> furthermore< /RTI> , RTI <ID=18 was described.5> that< /RTI> with Tributyrin no sturdy emulsions with small <RTI ID=18.6> particle size< /RTI> to manufacture is.

<RTI ID=18.7> surprisingly< /RTI> now RTI <ID=18 became.8> according to invention< /RTI> <RTI ID=18.9> found that< /RTI> it <RTI ID=18.10> possible< /RTI> is to receive in Triglyceriden, which prefers fatty acids with 2-22 carbon atoms, 4-20 carbon atoms contained solving a sufficient quantity of Taxanen in order therapeutically effective concentrations of these Taxane and to manufacture pharmaceutical compatible and effective emulsions.

In order to solve Taxane in the necessary concentrations, the Taxane becomes into the desired Triglyceride, and/or.

Mixtures from different Triglyceriden given and the mixture, if necessary under <RTI ID=18.11> agitating,< /RTI> heats, to itself the Taxan up <RTI ID=18.12> solved< /RTI> has. The Taxan becomes alternative, if necessary under <RTI ID=18.13> agitating,< /RTI> into or the Triglycerid heated up already warmed up and/or. Mixture from Triglyceriden given. The Triglycerid should not <RTI ID=18.14> over< /RTI> the melting point of the Taxans, that for example with Paclitaxel with approx. <RTI ID=18.is appropriate> for 15 <,210> /RTI C, to be heated up.

The lower the number of carbon atoms of the fatty acids in the Triglycerid used in each case is, the more easily separates the Taxan with heating up. So <RTI ID=19.1> already< leaves itself> Paclitaxel to /RTI with <RTI ID=19.2> 60-90 </RTI> C in <RTI ID=19.3> Tributyrin solves, during< /RTI> it to <the RTI ID=19.4> release< /RTI> in Tricaprylin and/or Tricaprin is favourable, on approx. 110< RTI ID=19.to heat up> 5,130< C> /RTI.

Also the boiling point or the used Triglyceride, that for example for Tributyrin with approx. <RTI ID=19.is appropriate> for 6,130< C> /RTI, should with <the RTI ID=19.7> release< /RTI> (r) of the Taxans (E) not to be exceeded. Generally the active substances under RTI <ID=19 become.8> agitating< /RTI> at temperatures between <RTI ID=19.9> 60 and 160 C solved,< /RTI> whereby <the RTI ID=19.10> necessary< /RTI> temperature is dependent from the number of carbon atoms of the RTI ID=19 contained in <the Triglyceriden.11> fatty acids.</RTI>

For each <RTI ID=19.12> more highly< /RTI> the number of carbon atoms, the <RTI ID=19.13> more highly< /RTI> to <RTI ID=19.Temperature> used< 14> release /RTI. In Tributyrin <RTI ID=19./RTI> leaves itself< 15> for example Paclitaxel with approx. <RTI ID=19.16> 60-100 C< /RTI> well solve.

The solution procedure takes place best under exclusion from oxygen, z. B. in <a RTI ID=19.17> nitrogen atmosphere< to avoid> /RTI around decomposition due to oxidation procedures.

It is favourable to pay attention during the entire manufacture procedure to absence from oxygen to. It is also <RTI ID=19.18> possible,< /RTI> the used Taxan first in a Triglycerid of fatty acids with few carbon atoms, z. B. Tributyrin at relatively low temperatures, for example <RTI ID=19.19> 70-100 C< /RTI> to <RTI ID=19.20> solves< /RTI> and then further Triglyceride to admit.

By <the RTI ID=19.21> release< /RTI> in the heat can be reached problem-free therapeutically relevant concentrations of the Taxane in the Triglyceriden.

Concentration <RTI ID=19.22> solvents< /RTI> Paclitaxel/g at least. 40 <RTI ID=19.23> mg/g< /RTI> Tributyrin at least. 20 <RTI ID=19.24> mg/g< /RTI> Tricaproin at least. 15 <RTI ID=19.25> mg/g< /RTI> Tricaprylin at least. 15 <RTI ID=20.1> mg/g< /RTI> Mittelkettige Triglyceride <RTI ID=20.2> (C6-C12,< /RTI> predominantly C8-C10) at least. 4 <RTI ID=20.3> mg/g Sojaöl< /RTI> at least. 8 <RTI ID=20.4> mg/g MCT-Ö1/Sojaöl< /RTI> (in <the RTI ID=20.5> relationship< /RTI> 1: 1) <The RTI ID=20.6> solved< /RTI> quantities are sufficient, around the desired therapeutically effective concentrations in <the RTI ID=20.to reach> 7< /RTI> according to invention emulsion.

After the cooling of the Triglyceride and/or. Oils with that therein <RTI ID=20.>RTI< ID=20> shows up 8 solved </RTI Taxanen.9> surprisingly,< /RTI> that the Taxane also at room temperature in solution remain problem-free and not to fail, <for RTI ID=20.10> periods<, > so far over 19 months, long over /RTI. The past statements that itself Taxane in Triglyceriden and/or oils not sufficiently <RTI ID=20.11> does not solve< to reach> /RTI around therapeutic concentrations is applicable therefore.

The Taxane containing Triglyceride cooled down on 20-60 C is filtered, over possibly. to remove existing particles.

Production of the emulsion consisting of a mixture, of <RTI ID=21.1> 3-sn-Phosphatidylcholin< /RTI> (z. B. out), sodium oleate, Glycerin and water become by <RTI ID=21.2> agitating< /RTI> with a Ultra Turrax raw emulsions manufactured at a temperature of approx. <RTI ID=21.3> 40-70 C.</RTI> into this raw emulsion is adjusted if necessary, preferentially now the Taxane containing Triglyceridlösung and water given, the pH value by addition by alkali salts by fatty acids to 5-9 to 6-8.

The mixture, which now Taxane, Triglyceride, 3-sn Phosphatidylcholin, water, a Isotonisierungsmittel such as z.

B. Glycerin and alkali salts of fatty acids contain if necessary, become by <RTI ID=21.It homogenizes> 4< agitating> /RTI with a Ultra Turrax whereby a raw emulsion will receive. The mixture is stopped in such a way by addition by water, <RTI ID=21.5> that< /RTI> of the Triglyceridgehalt <RTI ID=21.6> 1-60< /RTI> Gew% amounts to.

The raw emulsion becomes now in a Hochdruckhomogenisator with three pistons with <RTI ID=21.7> pressures< /RTI> between 100-700 bar, preferentially between 300-600 bar, if necessary several times, until an emulsion is present, in that the RTI <ID=21 homogenizes.8> particle size< /RTI> of at least 97 <RTI ID=21.below> 5< Micron> , preferentially under 1 , 5 Micron is to 9 % /RTI of all fat particles.

Afterwards the emulsion with water is diluted on the desired concentration and in ampuls or bottles <RTI ID=21.10> filled up< /RTI> and heat-sterilizes. Thereby the sterilization is preferential in a so-called. Rotation autoclaves, in that the containers during the sterilization <RTI ID=21.11> over< /RTI> head to be rotated. This leads to a better heat transfer into <the RTI ID=21.12> containers.</RTI> thereby becomes the heating phase and <RTI ID=21.And>< the risk> of a RTI ID=21 shortens 13 <cooling phase /RTI.14> damage< /RTI> of contents <of the RTI ID=21.15> containers< /RTI> reduces. It is favourable, the entire manufacture procedure under exclusion of oxygen <RTI ID=21.to accomplish> 16.</RTI>

The following examples describe the pharmaceutical Darreichungsform according to invention and the procedure for their production in detail.

The invention is not however on it <RTI ID=22.1> limits.</RTI>

Example 1 production of an emulsion with Paclitaxel in <RTI ID=22.2> MCT oil< /RTI> and <RTI ID=22.3> Sojaöl< /RTI> 1000 mg Paclitaxel becomes under <RTI ID=22.4> agitating< /RTI> in 200 g of a Triglycerid mixture given, that from MCT-Ö1 (mittelkettige Triglyceride) with predominantly fatty acids with 8 and 10 carbon atoms and <RTI ID=22.5> Sojaöl< /RTI> in <the RTI ID=22.6> relationship< /RTI> 1: 1 exists. The mixture becomes under <RTI ID=22.7> agitating< /RTI> and Begasen with nitrogen on approx.

<RTI ID=22.8> 110-135 C< /RTI> heats up, until a to a large extent clear solution will receive.

Alternatively the Paclitaxel (1000 mg) can first in 100 g MCT-Ö1 with approx. <RTI ID=22.9> 110-135 </RTI> C <RTI ID=22.10> /RTI< become> solved and only thereafter <RTI ID=22.11> Sojaöl,< /RTI> heats up on approx. <RTI ID=22.12>,120 C,< /RTI> to be admitted.

One <RTI ID=22./RTI> on< approx.> leaves 13. <RTI ID=22.and> <a fat-resistant> sterilization filter with a Porengrösse of approx. filters 14 40-80 /RTI C cooling by. 50 Micron.

In a further <RTI ID=22.15> container< /RTI> is given now to 25 g Glycerin as well as 200 ml water and with nitrogen are begast, to which amounts to oxygen content less than 0, 5 mg/l. Now 12 g become (iodine number of 60-70) with a content of 3-sn Phosphatidylcholin of approx. 80 <RTI ID=22.16> %< /RTI> and approx. 12 <RTI ID=22.17> % < /RTI> Phosphatidylethanolamin admitted and 0, 4 g sodium oleate.

By strong <RTI ID=22.18> agitating< /RTI> with a Ultra Turrax becomes at a temperature of approx. <RTI ID=22.19> 40-60 </RTI> C a raw emulsion manufactured.

Now the Paclitaxel becomes containing <RTI ID=22.20> Triglycerid solution< /RTI> admitted and further 10 minutes with a Ultra Turrax strongly <RTI ID=22.21> agitated.</RTI> the pH value is examined and should lie between 5 and 9, preferentially between 6-8, especially prefers between 6, 5 and 7, 5.

The received raw emulsion becomes by a fat-resistant high-grade steel filter <RTI ID=22.22>(Porengrösse</RTI> zwischen 5-50 Mikron) filtriert und anschliessend mit einem 2-Stufen-Hochdruck-Homogenisator mit drei Kolben homogenisiert bei <RTI ID=22.23> pressures< /RTI> between 100-600 bar. The procedure of the homogenization is so often repeated, until the desired <RTI ID=23.1> particle size< /RTI> is reached. Less than 1 <RTI ID=23.2> %< /RTI> of the particles should be larger than 4 Micron. <RTI ID=23.3> in< /RTI> means the diameter of the particles 0, 2-0, 6 Micron amounts to.

Around a well applicable <RTI ID=23.4> particle size< /RTI> to reach, is it generally <RTI ID=23.5> necessarily,< /RTI> the procedure of the homogenization approx. to repeat 3-6 times. After each homogenizing procedure the emulsion on RTI <ID=23 should.6> 30-60 </RTI> C <RTI ID=23.7> /RTI< become> cooled down. The emulsion becomes now in 560 ml oxygen-free water <RTI ID=23.8> for< /RTI> injection purposes given. It is begast again with nitrogen, to which oxygen content below mg/l is 0, 5.

Before the filling in 250 ml Glasflaschen by high-grade steel filter with a middle Porengrösse is filtered of 5 Micron. The filtration pressure should not thereby 0, 2 bar <RTI ID=23.9> exceeds< to prevent> /RTI around breaking the emulsion.

<The RTI ID=23.10> particle size< /RTI> and the particle distribution <of RTI ID=23.11> can <be determined> /RTI for example by means of microscope or Coulter Counter.

Particle size number of the particles < 0, 2 Micron 34% 0, 2-0, 5 Micron 43% 0, 5-0, 9 Micron 14% 0, 9-1, 2 Micron 6 <RTI ID=23.12> %< /RTI> 1, 2-1, 9 Micron 2 <RTI ID=23.13> %< /RTI> 1, 9-2, 2 Micron under 1% 2, 2-2, 5 Micron under 1% 2, 5-3, 2 Micron under 1 <RTI ID=23.14> %< /RTI> > 3, 2 Micron under 1 <RTI ID=23.15> %< /RTI> the emulsion becomes in 250 ml-Glasflaschen <RTI ID=23.16> filled up.</RTI> the bottles are begast before the filling with nitrogen.

It is favourable, the used nitrogen on minus <RTI ID=23.to cool down> 17 <20-30> /RTI C, so that the nitrogen sinks more easily on the soil of the bottle. Also during the filling up procedure the bottles should be begast further with nitrogen.

The received emulsion heat-sterilized with <RTI ID=24.1>,121 ' C for< /RTI> 20 minutes. Thereby a so-called rotation autoclave is used favourably, in that the bottles <RTI ID=24.2> during< /RTI> of the sterilization <RTI ID=24.3> over< /RTI> head rotate. Thus becomes <the RTI ID=24.It decreases> and< avoided> 4 rackings /RTI and Abkühlen necessary time that itself <the RTI ID=24.5> particle size< /RTI> changes.

The particle distribution according to the sterilization is as follows: <RTI ID=24.6> particle size< /RTI> number of the particles < 0, 2 Micron 25 <RTI ID=24.7> %< /RTI> 0, 2-0, 5 Micron 46% 0, <RTI ID=24.8>,5-0,< /RTI> 9 Micron 19% 0, 9-1, 2 Micron 6 <RTI ID=24.9> %< /RTI> 1, 2-1, 5 Micron 2 1, 5-1, 9 Micron under 1% 1, 9-2, 2 Micron under 1% 2, 2-3, 2 Micron under 1 <RTI ID=24.10> %< /RTI> > 3, 2 Micron 0 <RTI ID=24.11> %< /RTI> the sterilization leads therefore to no substantial change <of the RTI ID=24.12> particle size< /RTI> and Partikelverteilung. The emulsion is stable. To one year's storage at ambient temperature no substantial RTI <ID=24 points itself.13> change< /RTI> <of the RTI ID=24.14> particle size< /RTI> and Partikelverteilung.

One receives a sturdy emulsion with the following composition per 100 ml: Paclitaxel: 100 mg <RTI ID=24.15> Sojaöl< /RTI> plus MCT-Ö1: 20 g : 1, 2 g Glycerin: 2, 5 g sodium oleate: 40 mg as well as water ad 100 ml 250 to 500 ml the emulsion <RTI ID=24.16> knows< /RTI> now slowly <RTI ID=24.17> over< /RTI> 3-10 Studen <RTI ID=24.18> /RTI< become> infused, whereby a therapeutically effective quantity of Paclitaxel is supplied.

Example 2 the procedure of the example 1 is repeated, whereby instead of Paclitaxel now 800 mg Docetaxel are used. One receives a pharmaceutical Darreichungsform with the following composition per 100 ml: Docetaxel 80 mg <RTI ID=25.1> Sojaöl< /RTI> 10 g MCT-Ö1 10 g 1, 2 g Glycerin 2, 5 g sodium oleate 40 mg water ad 100 ml example 3 60 g Tributyrin become under <RTI ID=25.2> agitating< /RTI> on approx. <RTI ID=25.3> 70-90 C< /RTI> warms up under nitrogen. 1000 mg Paclitaxel are admitted and further with <RTI ID=25.4> 70-90 C agitated< one receives> to /RTI to a clear solution. One <RTI ID=25./RTI> on< approx.> leaves 5. <RTI ID=25.6> 30-60 C cooling.</RTI>

The further production takes place similar to the example <RTI ID=25.7> I.</RTI>

It will receive an emulsion according to invention with the following composition per 100 ml: Paclitaxel 100 mg Tributyrin 6, 0 g 1, 2 g Glycerin 2, 5 g sodium oleate 40 mg water <RTI ID=25.8> for< /RTI> injection purposes ad 100 ml example 4 30 g Tributyrin and 70 g <RTI ID=25.9> MCT oil< /RTI> (with predominantly fatty acids with 8 and 10 carbon atoms, i.e. Capryl and Caprinsäure) becomes on approx. <RTI ID=25.10> 110-130 </RTI> C under <RTI ID=25.11> agitating< /RTI> warms up and 800 mg Paclitaxel under <RTI ID=26.1> agitating< /RTI> admitted, until a clear <RTI ID=26.Originates in> to 2< solution> /RTI. One <RTI ID=26./RTI> on< 30-60> C cooling leaves and proceeds 3 in the further production similar to example 1, whereby however by Sojalecithin with a content at <RTI ID=26.4> 3-sn-Phosphatidylcholin< /RTI> of approx. 70-80 <RTI ID=26.one replaces> to 5< %> /RTI.

Instead of sodium oleate potassium oleate is used.

One <RTI ID=26./RTI> receives< 6> an emulsion according to invention with the following composition per 100 ml: Paclitaxel 80 mg Tributyrin 3 g <RTI ID=26.7> MCT oil< /RTI> 7 g Sojalecithin 1, 2 g Glycerin 2, 5 g potassium oleate 40 mg water <RTI ID=26.8> for< /RTI> injection purposes ad 100 ml example 5 ,800 mg Paclitaxel become under <RTI ID=26.9> agitating< /RTI> with 120-140 C in 150 g <RTI ID=26.10> MCT oil< /RTI> solved. The used MCT-Ö1 contains 65% Caprylsaure (C8) and 32% Caprinsäure as Triglyceride.

Besides still small quantities of RTI ID=26 are <as Triglyceride.11> Capronsäure,< /RTI> Laurinsäure and Myristinsäure contain. Still 0, 6 g free RTI <ID=26 become.12> oleic acid< /RTI> admitted. It is manufactured similar to example 4, whereby however instead of potassium oleate potassium hydroxide is used for the pH attitude. Thus develops in situ potassium oleate as in example 4. <A RTI ID=26.ml>< one receives> to 13 /RTI according to invention emulsion with the following composition per 100.

Paclitaxel 100 mg MCT-Ö1 15 g Glycerin 2, 5 g Sojalecithin 1, 2 g potassium oleate 69 mg water <RTI ID=26.14> for< /RTI> injection purposes ad 100 ml example 6 ,500 mg Paclitaxel become under <RTI ID=27.1> agitating< /RTI> and under nitrogen atmosphere consisting in a Triglyceridgemisch, of 100 g MCT-Ö1 and 50 g <RTI ID=27.2> Fischöl< /RTI> with a content of altogether 40 <RTI ID=27.3> %< /RTI> <RTI ID=27.4> Omega-3-Fettsäuren,< /RTI> in particular Eicosapentaensäure and Docoshexanensäure, with approx. <RTI ID=27.5> 130-150 </RTI> C solved. That oxygen content of the Triglyceride was adjusted before by Begasen with nitrogen to under 0, 5 mg/l.

<RTI ID=27.6> additional< /RTI> were admitted to 10 mg Vitamin E.

The further manufacturing process takes place according to example <RTI ID=27.7> I.</RTI> it will receive an emulsion according to invention with the following composition per 100 ml.

Paclitaxel 50 mg MCT-Ö1 10 g <RTI ID=27.8> Fischöl< /RTI> 5 g Glycerin 2, 5 g 1, 2 g sodium oleate 40 mg Vitamin E 10 mg water <RTI ID=27.9> for< /RTI> injection purposes ad 100 ml

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Patent claims 1. Taxane containing pharmaceutical preparation in form <of a RTI ID=28.1> oil in water emulsion,< /RTI> thereby characterized, <RTI ID=28.2> that< /RTI> it at least a Taxan, at least a Triglycerid of fatty acids with 2-22 carbon atoms, 3-sn Phosphatidylcholin and/or Phosphatidylethanolamin and alkali salts of free fatty acids and water, however essentially no synthetic not ionischen emulsifying agents, <RTI ID=28.3> contains.</RTI>

2. Taxane containing pharmaceutical preparation according to requirement <RTI ID=28.4> 1,< /RTI> thereby characterized, <RTI ID=28.5> that< /RTI> the pharmaceutical preparation is present as pharmaceutical compatible oil in water emulsion to the intravenous infusion.

3. Taxane containing pharmaceutical preparation according to requirement 1 or 2, by it characterized, <RTI ID=28.6> that< /RTI> <the RTI ID=28.7> particle size< /RTI> of the fat particles than 5 Micron is predominantly smaller.

4. Taxane containing pharmaceutical after preparation or several the preceding <RTI ID=28.8> requirements,< /RTI> thereby characterized, <RTI ID=28.9> that< /RTI> <the RTI ID=28.10> particle size< /RTI> of the fat particles on the average between 0, 2 and 1 Micron <RTI ID=28.11> amounts to.</RTI>

5. Taxane containing pharmaceutical after preparation or several of the preceding requirements, by the fact characterized that as Taxane Paclitaxel and/or Docetaxel are used.

6. Taxane containing pharmaceutical after preparation or several of the preceding requirements, by the fact characterized that the Taxane in a pharmaceutical effective and contractual concentration of 0, 1 to 3 is present mg/ml, preferentially from 0, 2 to 1, 5 mg/ml.

7. Taxane containing pharmaceutical after preparation or several the preceding <RTI ID=29.1> requirements,< /RTI> thereby characterized, <RTI ID=29.2> that< /RTI> the Triglyceride from <RTI ID=29.3> fatty acids< /RTI> with 2 to 22 carbon atoms, preferentially with 4-20 carbon atoms exist.

8. Taxane containing pharmaceutical after preparation or several the preceding <RTI ID=29.4> requirements,< /RTI> by the fact characterized that as Triglyceride Tributyrin and/or Tricaproin and/or Tricaprylin and/or Tricaprin and/or mittelkettige Triglyceride with predominantly Caprylsäure and Caprinsäure and/or <RTI ID=29.5> Sojaöle< /RTI> and/or Olivenöle, and/or <RTI ID=29.6> thistle oils< /RTI> and/or <RTI ID=29.7> corn germ oils< /RTI> and/or <RTI ID=29.8> wheat germ oils< /RTI> and/or <RTI ID=29.9> Sonnenblumenöle< /RTI> and/or <RTI ID=29.10> Fischöle< /RTI> and/or Triolein and/or <RTI ID=29.11> Trilinolein< /RTI> is contained.

9. Taxane containing pharmaceutical after preparation or several of the preceding requirements, by the fact characterized that the Triglyceride in a portion from 1 to 60 <RTI ID=29.4-40> RTI ID=29< prefer> 12 % <, /RTI.13> %< /RTI> of the total weight in the pharmaceutical preparation are present.

10. Taxane containing pharmaceutical after preparation or several of the preceding requirements, thereby characterized, <RTI ID=29.14> that< /RTI> the 3-sn-Phosphatidylcholin is present in the form of 3-sn Phosphatidylcholin containing substances and that preferably the 3-sn-Phosphatidylcholin containing substance is and/or Sojalecithin (Sojaphosphatid).

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11. Taxane containing pharmaceutical after preparation or several of the preceding requirements, by the fact characterized that the used contains and/or Sojalecithin a portion of 60 to 90 Gew% 3-sn-Phosphatidylcholin, whereby is particularly preferential.

12. Taxane containing pharmaceutical after preparation or several of the preceding requirements, by the fact characterized that the used 3-sn-Phosphatidylcholin is partial or completely hydrogenated.

<RTI ID=30.1> 13.</RTI> Taxane containing pharmaceutical after preparation or several of the preceding requirements, thereby characterized, <RTI ID=30.2> that< /RTI> the content of 3-sn-Phosphatidylcholin in the pharmaceutical preparation 0, 2-4 <RTI ID=30.0>, 4< 2> , 5 Gew% RTI ID=30 prefer 3 Gew% <, /RTI.4> /RTI< amounts to> and that the content of the 3-sn Phosphatidylcholin containing substances in the pharmaceutical preparation 0, 4-7, 0 <RTI ID=30.0>, RTI< ID=30> prefers 5 Gew% <, /RTI.6> 6< /RTI> 4 Gew% amounts to.

14. Taxane containing pharmaceutical after preparation or several of the preceding requirements, by the fact characterized that as pharmaceutical compatible free fatty acids <RTI ID=30.7> satisfied< /RTI> and/or <RTI ID=30.8> insatiated< /RTI> fatty acids and/or alkali salts, preferentially with 6-24 carbon atoms, contained are, whereby preferably as pharmaceutical <RTI ID=30.9> compatible< /RTI> free fatty acids <RTI ID=30.10> oleic acid< /RTI> and/or Palmitinsäure and/or Palmitoleinsäure and/or Linolsäure and/or Linolensäure and/or their alkali salts, potassium and/or sodium salts prefer being used.

15. Taxane containing pharmaceutical after preparation or several of the preceding requirements, by the fact

characterized that the content of free fatty acids and/or their alkali salts prefers 0, 01-0, 2 Gew%, 0, 02-0, 1 Gew% amounts to.

16. Taxane containing pharmaceutical after preparation or several of the preceding requirements, thereby characterized, <RTI ID=31.1> that< /RTI> contains the pharmaceutical preparation additionally of substances such as Glycerin and/or glucose and/or Sorbit and/or Fruktose in such a quantity, in order to make the pharmaceutical preparation blood isotone.

17. Taxane containing pharmaceutical after preparation or several the preceding <RTI ID=31.2> requirements,< /RTI> thereby characterized, <RTI ID=31.3> the fact that< /RTI> the pharmaceutical preparation Phosphatidylethanolamin in a quantity of 0, 01-2, 0 Gew, - contains %.

18. Procedure for the production of the Taxane after containing pharmaceutical preparation or several the preceding <RTI ID=31.4> requirements,< /RTI> thereby characterized, <RTI ID=31.>the Taxane< in> Triglyceriden of fatty acids with 2-22 carbon atoms prefers 5 that /RTI, 4-20 carbon atoms, <RTI ID=31.6> solved< /RTI> will be emulsified and afterwards with 3-sn-Phosphatidylcholin and/or Phosphatidylethanolamin and alkali salts of free Fettäuren and water in actually well-known way.

19. Procedure for the production of the Taxane containing pharmaceutical preparation according to requirement 18, by it characterized, <RTI ID=32.1> that< /RTI> the Taxane before emulsifying in the Triglyceriden at temperatures of more than <RTI ID=32.2> 60 C,< /RTI> prefers between <RTI ID=32.3> 70 C< /RTI> and 150 C, to be solved.

20. Procedure for the production of the Taxane after containing pharmaceutical preparation or several the preceding <RTI ID=32.4> requirements,< /RTI> thereby characterized, <RTI ID=32.5> that< /RTI> the Taxane in Triglyceriden with fatty acids with 4 to 6 carbon atoms at temperatures between 70 to <RTI ID=32.6>,110 </RTI> C <RTI ID=32.7> /RTI< become> solved.

21. Procedure for the production of the Taxane after containing pharmaceutical preparation or several the preceding <RTI ID=32.8> requirements,< /RTI> thereby characterized, <RTI ID=32.9> that< /RTI> the Taxane in Triglyceriden with fatty acids with more than 8 carbon atoms at temperatures of <RTI ID=32.10>,100 C< /RTI> and over it to be solved.

22. Procedure for the production of the Taxane after containing pharmaceutical preparation or several of the preceding requirements, by the fact characterized that the Taxane prefers RTI ID=32 to emulsifying in the Triglyceriden of fatty acids with 2-22 carbon atoms , <4-20 carbon atoms.11> completely< /RTI> <RTI ID=32.12> solved< /RTI> and afterwards with assistance of 3-sn-Phosphatidylcholinen and/or free fatty acids and/or their alkali salts in water to a raw emulsion to be emulsified and the mixture afterwards to an emulsion, prefers with <a RTI ID=32.13> particle size< /RTI> of less than 5 <RTI ID=32.14> over,< /RTI> in particular under 1, <RTI ID=32.15> 5< /RTI> Micron, one homogenizes.

23. After procedure or several of the preceding requirements, by the fact characterized that the alkali salts of free <RTI ID=33.1> fatty acids< /RTI> in situ by conversion of alkali hydroxides with free <RTI ID=33.2> fatty acids< /RTI> to be manufactured.

24. After procedure or several the preceding <RTI ID=33.3> requirements,< /RTI> thereby characterized, <RTI ID=33.4> that< /RTI> the mixture from Taxanen, Triglyceriden, Phosphatidylcholin and water already 0, 01-0, 15 <RTI ID=33.and> prefers< this> mixture by means of an alkaline solution before emulsifying to a pH value of 5 10 contains 5 % /RTI at free natural fatty acids and/or their alkali salts, 7-9, is adjusted, which causes also the formation of the alkali salts.

25. After procedure or several the preceding <RTI ID=33.6> requirements,< /RTI> thereby characterized, <RTI ID=33.7> that< /RTI> the alkali salts of free fatty acids are used, in order the emulsion on a pH value of 5-10, prefer 7, 0 9, 0, to adjust.

26. After procedure or several the preceding <RTI ID=33.8> requirements,< /RTI> by the fact characterized that for the production of the pharmaceutical preparation essentially oxygen-free solutions are used.

27. After procedure or several of the preceding requirements, thereby characterized, <RTI ID=33.9> that< /RTI> <RTI ID=33.10> additionally< /RTI> Glycerin and/or glucose and/or Sorbit and/or Xylit and/or Fruktose in quantities to be used, which are suitable to make the pharmaceutical preparation isotone.

28. After procedure or several the preceding <RTI ID=34.1> requirements,< /RTI> by the fact characterized that by intensive <RTI ID=34.2> agitating< /RTI> first a raw emulsion is manufactured and afterwards <the RTI ID=34.3> final< /RTI> emulsifying in a high pressure Homogenisator with <RTI ID=34.4> pressures< /RTI> between 100 ,600 bar takes place, whereby preferably high pressure Homogenisator possesses at least three pistons.

29. After procedure or several the preceding <RTI ID=34.5> requirements,< /RTI> by the fact characterized that the sterilization of the pharmaceutical preparation takes place via heat sterilization in rotation autoclaves.

30. Use after the pharmaceutical preparation or several the preceding <RTI ID=34.6> requirements< /RTI> to intravenous application, preferably to the intravenous injection and/or infusion.